REMARKS/ARGUMENTS

Prior to the present amendment, Claims 33, 38-40 and 44-53 were pending in this application. With this amendment, Claims 48-53 have been canceled without prejudice.

Claims 33, 38-40, and 44-47 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

Applicants note and appreciate the withdrawal of the earlier objections and rejections under 35 U.S.C. §112, second paragraph, 35 U.S.C. §102(a), and 35 U.S.C. §112, first paragraph, for lack of written description.

The remaining objections and rejections of Claims 33, 38-40 and 44-53 under 35 U.S.C. §101 and under 35 U.S.C. §112, first paragraph, for lack of enablement, are addressed below.

I. Priority

Applicants thank the Examiner for granting the priority of the instant application as October 29, 1999.

II. Oath/Declaration

The Examiner maintains that the oath or declaration of the present application is defective because non-initialed and/or non-dated alteration have been made to the oath or declaration (for inventor Dan Eaton). More specifically, the Examiner alleges that "Applicant failed to note the conjunction of 'dated' and 'initialed' as one unit." The Examiner further contends, "The signature and date concerns the Oath/Declaration proper and not alterations which are covered by 37 C.F.R. §1.52(c)." (Page 4 of the instant Office Action).

Applicants respectfully disagree.

Applicants respectfully submit that 37 C.F.R. §1.52(c)(1) states:

> (c)(1) Any interlineations, erasure, cancellation or other alteration of the application papers filed must be made before the signing of any accompanying oath or declaration pursuant to §1.63 referring to those application papers and should be dated *and* initialed or signed by the applicant on the same sheet of paper. (Emphasis added).

Applicants respectfully submit that the Examiner has misinterpreted 37 C.F.R. §1.52(c) to simply require "dated and initialed" as a "one unit" requirement. Rather, Applicants submit that 37 C.F.R. §1.52(c)(1) has three requirements for an applicant making an alteration in the oath or declaration. First, the oath or declaration must be dated. Second, the oath or declaration must be initialed or signed. Finally, the date *and* initial or signature of the Applicant must be on the same sheet of paper.

Applicants note that inventor Dan Eaton initialed below the address change and dated the declaration on the same page. Although Dr. Eaton did not date the declaration next to his initial, Applicants submit that 37 C.F.R. §1.52(c)(1) does not require that the date be next to the initial. In fact, 37 C.F.R. §1.52(c)(1) only requires that the initial or the signature of the applicant be on the same page as the date and need not necessarily be adjacent to each other.

Nevertheless, without acquiescing to the Examiner's position in the current objection, and solely in the interest of expediting prosecution in this case, Applicants respectfully submit a new declaration which includes a substitute page reflecting the correct address for Dr. Dan Eaton that is dated and signed by Dr. Dan Eaton.

Applicants note that the signatures of the remaining inventors are as originally submitted in the present application and the new declaration was not executed by the remaining inventors.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the objection.

III. Claim Objections

Claim 48 is objected to because of alleged typographical errors "of an at" and "use." Claim 48 is further objected to because the recitation of "a complement" is allegedly unclear."

Without acquiescing to the Examiner's position in the current rejections, and without prejudice to further prosecution of the subject-matter in one or more continuation or divisional applications, Applicants have canceled Claims 48-53.

Accordingly the rejection of Claim 48 is moot, and Applicants respectfully request the Examiner to withdraw the objection.

IV. Claim Rejections Under 35 U.S.C. §101 and §112, First Paragraph (Enablement)

Claims 33, 38-40, and 44-53 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well-established utility." (Page 5 of the instant Office Action). The Examiner alleges that "[f]urther research needs to be done to determine whether the small increase in PRO1780 DNA supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial" (Page 6 of the instant Office Action).

Claims 33, 38-40, and 44-53 further remain rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility one skilled in the art clearly would not know how to use the invention." (Page 5 of the instant Office Action).

Applicants respectfully disagree and traverse the rejections.

Applicants submit that the cancellation of claims 48-53 renders the rejection of these claims moot.

Applicants submit, for the reasons set forth below, that the specification discloses at least one credible, substantial and specific asserted utility for the PRO1780 polynucleotide.

Utility – Legal Standard

According to 35 U.S.C. § 101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson*[1] the Supreme Court held that the quid pro quo contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or

[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

her invention, i.e. a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

Later, in *Nelson v. Bowler*[4] the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

In *Cross v. Iizuka*[6] the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between."[7] The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "in vitro testing, may establish a practical utility."[8]

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial

---

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

burden that applicants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11], [12]

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines")[15], which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

---

[10] *Ibid.*

[11] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[12] *See also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[15] 66 Fed. Reg. 1092 (2001).

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "'substantial'" utility.'"[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility – Application of Standard

The specification provides sufficient disclosure to establish a specific, substantial and credible utility for the claimed polynucleotides for the reasons previously set forth in the Applicants' response filed on January 14, 2005, and below.

The Examiner alleges that "SEQ ID NO:281 is elevated in a relative, non-quantitative assay of genes from a lung tumor sample." Furthermore, the Examiner alleges, "Overexpression of a single gene is not necessary or sufficient to indicate whether the tumor is malignant or benign, establish vascularization, or its potential for metastasis." Finally, the Examiner contends, "the commercially available tumor tissues used in the Specification lack any detailed information about the tumors used." (Page 6 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection.

First of all, Applicants respectfully submit that the gene amplification assay is well-described in Example 143 of the present application. As previously discussed in the Applicants' response of January 14, 2005, the nucleic acids encoding PRO1780 had a ΔCt value of > 1.0,

---

[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II (B)(1).

which is a **more than 2-fold increase**, for primary lung tumors LT4, LT7 and LT22. Therefore, Applicants have clearly shown that the nucleic acid sequence of SEQ ID NO:281 is amplified in a well-established and quantitative assay.

Secondly, regarding the Examiner's assertion that "overexpression of a single gene is not necessary or sufficient to indicate whether the tumor is malignant or benign, establish vascularization, or its potential for metastasis", Applicants respectfully submit that the Examiner has not established a *prima facie* case for lack of utility for the nucleic acid sequence of SEQ ID NO:281.

MPEP §2107.02(IV) states, "To properly reject a claimed invention under 35 U.S.C. 101, the Office must: (A) make a *prima facie* showing that the claimed invention lacks utility, and (B) provide a sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing. *In re Gaubert*, 524 F.2d 1222, 1224, 187 USPQ 664, 666 (C.C.P.A. 1975)." Applicants note that the Examiner has not provided any evidentiary basis for Examiner's assertion indicating why overexpression of a single gene, SEQ ID NO:281 is not sufficient to indicate that SEQ ID NO:281 would be useful as a diagnostic marker of human lung cancer.

Further, Applicants respectfully submit, "There is no predetermined amount or character of evidence that must be provided by an applicant to support an asserted utility, therapeutic or otherwise. Rather the character and amount of evidence needed to support an asserted utility will vary depending on what is claimed." *Ex parte Feguson*, 117 USPQ 229 (Bd. App. 1957); *see also* M.P.E.P. §2107.02(VII). Furthermore, M.P.E.P. §2107.02(VII) states that

> the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. *Nelson v. Bowler*, 626 F.2d 853, 856-57, 206 USPQ 881, 883-34 (CCPA 1980).

Accordingly, Applicants respectfully submit that when the proper evidentiary standard is applied, overexpression of a single gene SEQ ID NO:281, based on the disclosure in the present specification, is sufficient to establish an asserted utility for the nucleic acid sequence of SEQ ID NO:281, for example, as a marker for the diagnosis of cancer.

In addition, contrary to the Examiner's assertion that the specification lacks any detailed information about the tumors used, Applicants respectfully submit that the specification clearly provides detailed information about the tumors used in the gene amplification assay. For example, the lung cancer samples and cancer cell lines in the gene amplification assay represent different types, stages and physiological conditions of lung tumors. For example, on page 331, line 37 of the specification states, "The primary lung cancers were obtained from individuals with tumors of the type and stage as indicated in Table 8." Further, on page 337, line 9, the specification discloses that Table 8 describes "T stage and N stage of various primary tumors which were used to screen the PRO polypeptide compounds of the invention."

Applicants respectfully submit that lung cancer staging is the process of finding out how localized or widespread the cancer is. Each stage describes how far the cancer has spread. A treatment and prognosis depend on the cancer's stage.

The system used to describe the growth and spread of non-small cell lung cancer (NSCLC) in the instant application is the TNM staging system. T stands for tumor (its size and how far it has spread within the lung and to nearby organs), N stands for spread to lymph nodes, and M is for metastasis (spread to distant organs). In TNM staging, information about the tumor, lymph nodes, and metastasis is combined and a stage is assigned to specific TNM groupings. The grouped stages are described using the number 0 and Roman numerals from I to IV (1 to 4).

Accordingly, Table 7 also shows that these tested lung tumors and tumor cell lines are from various growth stages, such as IA, IIA, IIIA, IB, IIB, etc., or T1, T2, or T3, or N0, N1, or N2 stages.

Hence, Applicants submit that specification provides clear and detailed information about the tumors used in the gene amplification assay.

The Examiner alleges that Applicants' assertion of utility is "not specific because Applicant has not made a positive assertion of the polynucleotide of SEQ ID NO:281's or the polypeptide of SEQ ID NO:282's identity." (Page 6 of the instant Office Action). In particular, the Examiner asserts that Applicants have not taught whether SEQ ID NO:281 is a tumor suppressor gene or an oncogene.

The Examiner is applying an inappropriate test. The law clearly states that "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *Newman v. Quigg*, 11 USPQ2d 1340 (Fed. Cir. 1989). Accordingly, the disclosure or identification of such a mechanism is not required in order to establish the patentable utility of the polynucleotide of SEQ ID NO:281.

Applicants respectfully submit that the identification of SEQ ID NO:281 as a tumor suppressor or an oncogene is not relevant to its utility. Applicants respectfully submit that the present application discloses at least one credible, specific and substantial asserted utility for the nucleic acid sequence SEQ ID NO:281 encoding the PRO1780 polypeptide. The gene amplification data clearly shows that SEQ ID NO:281 was amplified in a number of primary lung tumors and thus would be useful as a diagnostic marker of human lung cancer That there is "sequence variance and diverse tissue distribution" of tumor related proteins and genes is also irrelevant. Applicants do not claim a random "tumor related gene," but a polynucleotide having a specific identified sequence, that of SEQ ID NO:281, as well as a specific identified expression pattern, that of being amplified in lung tumors.

The Examiner also alleges that Applicants' assertion of utility is not substantial because "it would constitute additional experimentation to first determine the identity of polynucleotide of SEQ ID NO:281, then to determine the use the nucleic acid of SEQ ID NO:281." Therefore, Examiner concludes that the asserted utility for the claimed nucleotide of SEQ ID NO:281 is not substantial "since significant further research would be required of the skilled artisan to determine what its properties are." (Pages 6-7 of the instant Office Action).

As discussed above, the law does not require Applicants to correctly set forth, or even know, how or why the invention works to in order to establish patentable utility. Accordingly, it is not necessary for Applicants to identify the biological properties or mechanism for the claimed biological function. The instant specification clearly discloses that the polynucleotide of SEQ ID NO:281 is amplified in a number of lung tumors.

Further, Applicants respectfully submit that the amplification of the nucleic acids in even one lung tumor provides specific and substantial utility for the nucleic acid as a diagnostic

marker of the type of lung tumor in which it was amplified. Applicants submit that the tumors listed in Table 8 are not similar tumors from different patients, but various types/classes of lung and/or colon tumors at different stages. Accordingly, a positive result from one tumor, where the nucleic acid was amplified, but not from other tumors, indicates that the nucleic acid can be used as a marker for diagnosing the presence of that kind of tumor in which it was amplified. Amplification of the nucleic acid would be indicative of that specific class of lung tumor, whereas absence of amplification would be non-conclusive.

Therefore, no further research is required to establish the patentable utility of the plynucleotide of SEQ ID NO:281. Accordingly, Applicants have demonstrated a credible, specific and substantial asserted utility for the polynucleotide of SEQ ID NO:281, for example as a marker for the diagnosis of cancer.

The Examiner asserts that the Declaration of Dr. Goddard filed under 37 CFR 1.132, is insufficient to overcome the rejection of claims 33, 38-40, and 44-53 based upon 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph. (See page 7 of the instant Office Action). The Examiner further asserts that "all that the specification does is present evidence that the DNA encoding PRO1780 is amplified in a variety of samples and invites the artisan to determine the significance of this increase." (Pages 7-8 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection.

Applicants have submitted Dr. Goddard's Declaration to show that the TaqMan real-time PCR method described in Example 143 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO1780 is a diagnostic marker of lung cancer.

The Examiner asserts that "[t]he PRO1780 gene ... has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1780 nucleic acid was amplified in two cancer samples, to a minor degree (about 2.5 fold)." (Page 7 of the instant Office Action). The Examiner further asserts that "[t]he Declaration does not provide data such that the examiner can

independently draw conclusions. Only Dr. Goddard's conclusions are provided in the declaration." (Page 8 of the instant Office Action).

Applicants first note that the PRO1780 nucleic acid was amplified in three cancer samples, the primary lung tumors LT4, LT7, and LT22, as shown in Table 8. Applicants next emphasize that the opinions expressed in the Goddard Declaration are all based on factual findings. Thus, Dr. Goddard explains that the TaqMan PCR assay is based on the principle that successful PCR yields a fluorescent signal due to Taq DNA polymerase-mediated exonuclease digestion of a fluorescently labeled oligonucleotide that is homologous to a sequence between two PCR primers. Further, Dr. Goddard explains that the assay is an extremely sensitive technique which leads to accurate determination of gene copy number. Dr. Goddard adds that the TaqMan PCR assay has been extensively and successfully used to characterize genes involved in cancer development and progression. For support, Dr. Goddard cites a number of references including a publication by Pennica *et al.* in which Dr. Goddard is a co-author of the paper. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Goddard would be considered reasonable and accurate by one skilled in the art.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.[18] "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument"[19] Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why

---

[18] *In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976) and *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985).

[19] *In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir 1996) (quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992)).

opinion evidence relating to a fact issue should not be considered by an examiner"[20]. Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines[21] which states, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." The statement in question from an expert in the field (the Goddard Declaration) states that "a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, for monitoring cancer development and/or for measuring the efficacy of cancer therapy." Therefore, barring evidence to the contrary regarding the above statement in the Goddard Declaration, this rejection is improper under both the case law and the Utility guidelines.

The Examiner cites Hu *et al.* in support of the assertion that "the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue." (Page 8 of the instant Office Action).

Applicants respectfully point out that the specification discloses gene amplification data, not transcript data. Hu *et al.* "compared the MedGene breast cancer gene list to a gene expression data set generated from a micro-array analysis comparing breast cancer and normal breast tissue samples." (See page 408, right column). Therefore, Applicants submit that the reference by Hu *et al.* only studies the statistical analysis of microarray data and not the gene amplification data. Hence, their findings would not be directly applicable to the gene amplification data. In addition, the Hu *et al.* reference does not show a lack of correlation between microarray data and the biological significance of cancer genes.

Further, the analysis by Hu *et al.* has certain statistical flaws. According to Hu *et al.*, "*different* statistical methods" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different

---

[20] *In re Alton, supra.*

[21] Part IIB, 66 Fed. Reg. 1098 (2001).

statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). It is well known in the art that various statistical methods allow different variables to be manipulated to affect the outcome. For example, the authors admit, "Initial attempts to search the literature using" the list of genes, gene names, gene symbols, and frequently used synonyms, generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors further admit that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* (Emphasis added). Hence, Applicants respectfully submit that in order to minimize the false positives and negatives in their analysis, Hu *et al.* manipulated various aspects of the input data.

Applicants further submit that the statistical analysis by Hu *et al.* is not a reliable standard because the frequency of citation only reflects the current research interest of a molecule but not the true biological function of the molecule. Indeed, the authors acknowledge that "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). It often happens in the scientific study that important molecules were overlooked by the scientific society for many years until the discovery of their true function. Therefore, Applicants submit that Hu *et al.* drew their conclusion based on a very unreliable standard and their research does not provide any meaningful information regarding the correlation between the microarray data and the biological significance.

Even assuming that Hu *et al.* provide evidence to support a true relationship, the conclusion in Hu *et al.* only applies to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and can not be generalized as a principle governing microarray study of breast cancer in general, let alone the various other types of cancer genes in general. In fact, even Hu *et al.* admit that "[i]t is likely that this threshold will change depending on the disease as well as the experiment. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column). Therefore, based on

these findings, the authors add, "This may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added).

Accordingly, Applicants respectfully submit that the Examiner has not shown a lack of correlation between microarray data and the biological significance of cancer genes.

The Examiner further cites Haynes *et al.* in support of the assertion that "what is often seen is a lack of correlation between DNA amplification and increased peptide levels." (Page 8 of the instant Office Action. Applicants respectfully submit that the claims of the instant application are directed to polynucleotides, not polypeptides. Thus the question of whether gene amplification is associated with increased protein expression is irrelevant. The claimed polynucleotides have utility because they are amplified in lung tumors, and thus may be used, for example, as diagnostic markers for lung cancer. The expression level of the encoded polypeptide is not relevant.

The Examiner asserts that the Declaration of Dr. Ashkenazi filed under 37 CFR 1.132, is insufficient to overcome the rejection of claims 33, 38-40, and 44-53 based upon 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph. (See page 10 of the instant Office Action). The Examiner refers to the discussion of gene product expression in paragraph 6 of the Ashkenazi Declaration, and agrees that "evidence regarding lack of over-expression would be useful. The Examiner asserts, however, that "there is no evidence as to whether the gene products (such as the PRO1780 polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not substantial." (Page 10 of the instant Office Action).

Applicants respectfully point out that paragraph 6 of the Ashkenazi Declaration considers whether gene amplification data are sufficient "to provide utility for the gene product (the encoded polypeptide)." The instant claims, however, are directed to polynucleotides, not polypeptides. In paragraph 5 of his Declaration, Dr. Ashkenazi states, "Even in the absence of overexpression of the gene product, amplification of a cancer marker gene - as detected, for example, by the reverse transcriptase TaqMan PCR or the fluorescence *in situ* hybridization

(FISH) assays - is useful in the diagnosis or classification of cancer, or in predicting or monitoring the efficacy of cancer therapy." Accordingly, one of ordinary skill in the art would not doubt that the amplified polynucleotides themselves have utility.

The Examiner further alleges, "One cannot determine from the data in the specification whether the observed 'amplification' of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates." (See page 7 of the instant Office Action). The Examiner further cites Sen to content that "chromosome aberrations known as aneuploidy are commonly observed in tumors." (Page 10 of the instant Office Action).

Applicants respectfully submit that it is known in the art that detection of gene amplification can be used for cancer diagnosis regardless of whether the increase in gene copy number results from intrachromosomal changes or from chromosomal aneuploidy. As explained by Dr. Ashkenazi in his Declaration,

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Hence, Applicants respectfully submit that gene amplification of a gene, whether by aneuploidy or any other mechanism, is useful as a diagnostic marker.

The Examiner asserts, "The instant disclosure is silent as to the actual biological activity or function of the polynucleotide of SEQ ID NO:281." The Examiner further alleges that "[b]ecause the instant specification does not provide some minimal context as to what altered levels of the polynucleotide of SEQ ID NO:281 mean the artisan can find no therapeutic utility for the claimed nucleic acid because significant and substantial further research would need to be performed in order to answer these simple but vital questions." Therefore, the Examiner concludes, "it is not clear how the skilled artisan would use the claimed nucleic acids for therapeutic uses." (Pages 11-12 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection.

As discussed above, Applicants respectfully submit that the gene amplification data shown in the present application clearly demonstrates that the nucleic acid of SEQ ID NO:281 is amplified in at least 3 primary lung tumors. Thus, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polynucleotides, for example, as a marker for the diagnosis of cancer.

Accordingly, based on this information one skilled in the art at the effective priority date of this application would have accepted that the nucleic acid encoding PRO1780 meets the utility requirement of the 35 U.S.C. §101 as a diagnostic marker for cancer. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polynucleotides.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejections under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

V. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 48-53 stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. In particular, the Examiner asserts that "the specification fails to provide any guidance for the successful isolation, and characterization of isolated nucleic acid comprising the SEQ ID NO;281 sequence or any variants, derivatives, and fragments thereof." (Page 13 of the instant Office Action).

Applicants submit that the cancellation of claims 48-53 renders the rejection of these claims moot.

Accordingly, the Examiner is respectfully requested to withdraw the present rejection.

VI. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 48-53 stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of adequate written description. In particular, the Examiner asserts that the specification "does not contain a written description of variants, derivatives, fragments, complements, or hybridizable fragments of the claimed polynucleotide." (Page 17 of the instant Office Action).

Applicants submit that the cancellation of claims 48-53 renders the rejection of these

claims moot.

Accordingly, the Examiner is respectfully requested to withdraw the present rejection.

VII. Claim Rejections Under 35 U.S.C. §102(b)

Claims 48-53 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Hillier *et al.* (EST 09-March-1998). Hillier *et al.* discloses a nucleic acid which shares 100% homology with SEQ ID NO:281 over 373 basepairs. The Examiner asserts that the nucleic acid disclosed by Hillier *et al.* is a "complement of" SEQ ID NO:281 that meets the limitations of claims 48-53.

Applicants submit that the cancellation of claims 48-53 renders the rejection of these claims moot.

Accordingly, the Examiner is respectfully requested to withdraw the present rejection.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C60**)

Respectfully submitted,

Date: July 8, 2005

By: _____
Barrie D. Greene (Reg. No. 46,740)

HELLER EHRMAN LLP
275 Middlefield Road
Menlo Park, California 94025-3506
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

SV 2127051 v1
7/7/05 3:50 PM (39780.2830)